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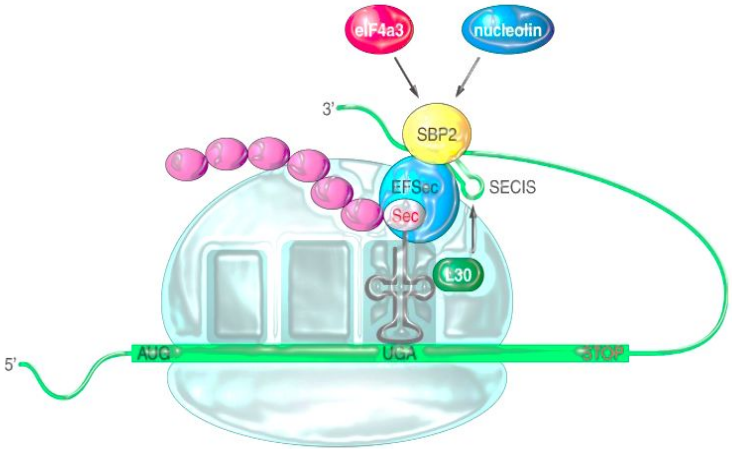
# INVESTIGATING THE STRUCTURAL AND FUNCTIONAL EFFECTS OF GLUTATHIONE PEROXIDASE VARIANTS.




Presenter
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13a Trobada de Joves Investigadors dels Països Catalans
31/01/2024

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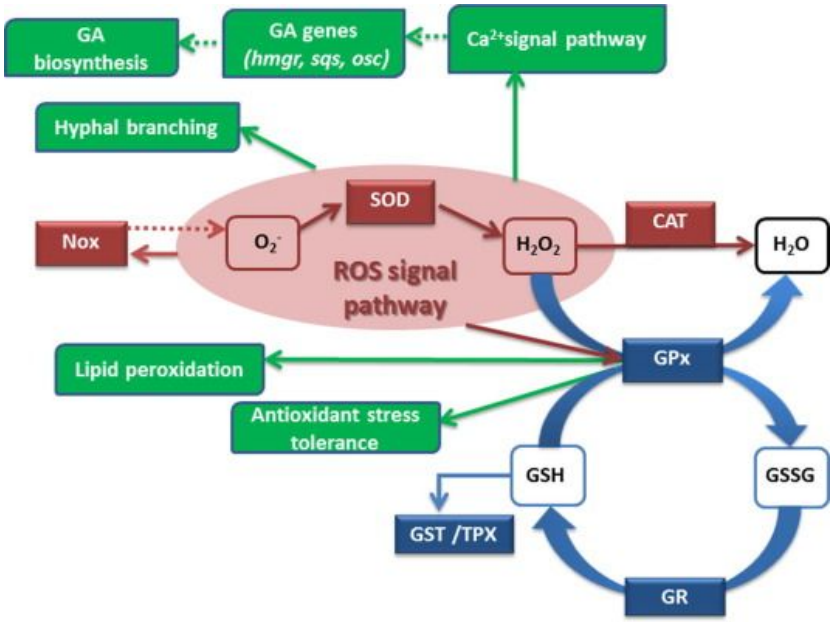
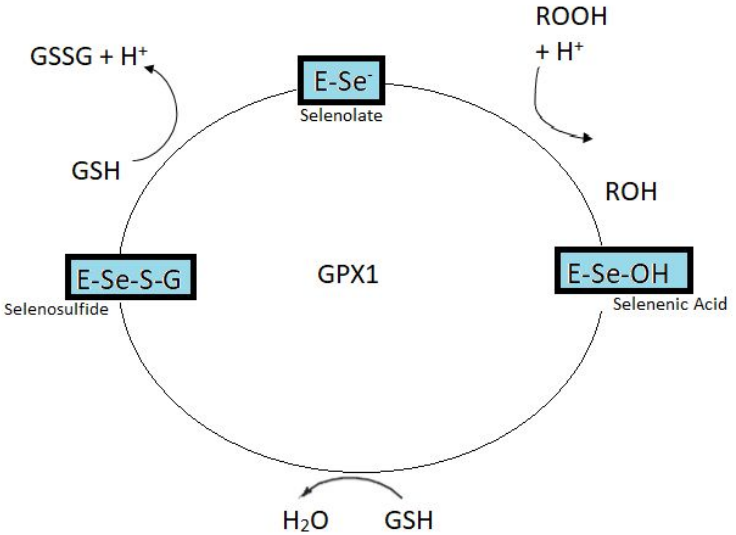
# Introduction

Glutathione Peroxidase (GPX)




Glutathione Peroxidase Function

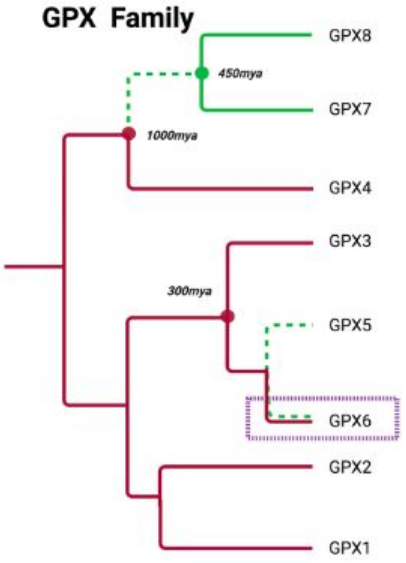



Catalytic Cycle

# Introduction

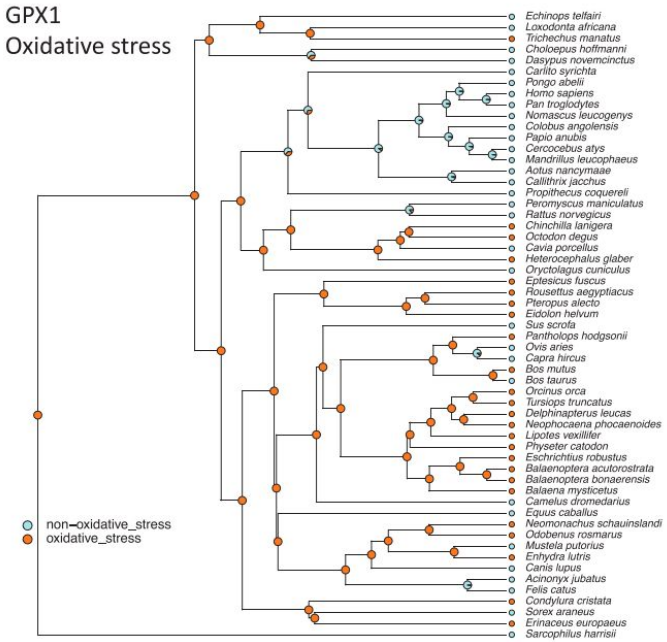
Similarity and Divergence in GPX


Structural Homology in GPX isoforms




The phylogeny of the GPX family in Eukaryotes

(based on Mariotti et al., 2012)

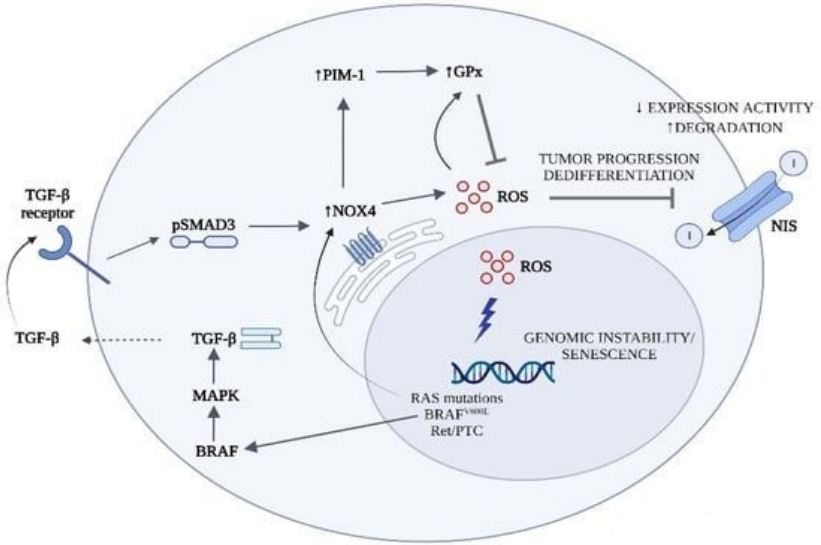



This indicate a convergent expansion of functional GPX1 in several independent lineages of oxidative stress-tolerant mammals

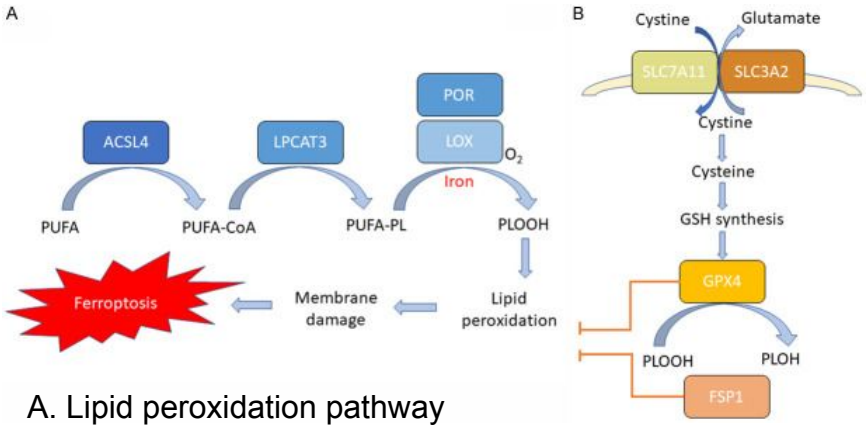
Tian R, Geng Y, Yang Y, Seim I, Yang G. Oxidative stress drives divergent evolution of the glutathione peroxidase (GPX) gene family in mammals. Integr Zool. 2021 Sep;16(5):696-711. doi: 10.1111/1749-4877.12521. Epub 2021 Jan 21. Erratum in: Integr Zool. 2022 May;17(3):479. PMID: 33417299.

# Introduction

GPX involvement in cancer




Schematic representation of the cellular mechanisms of reactive oxygen species (ROS) generation and effects




A. Lipid peroxidation pathway

B. Antioxidant pathway

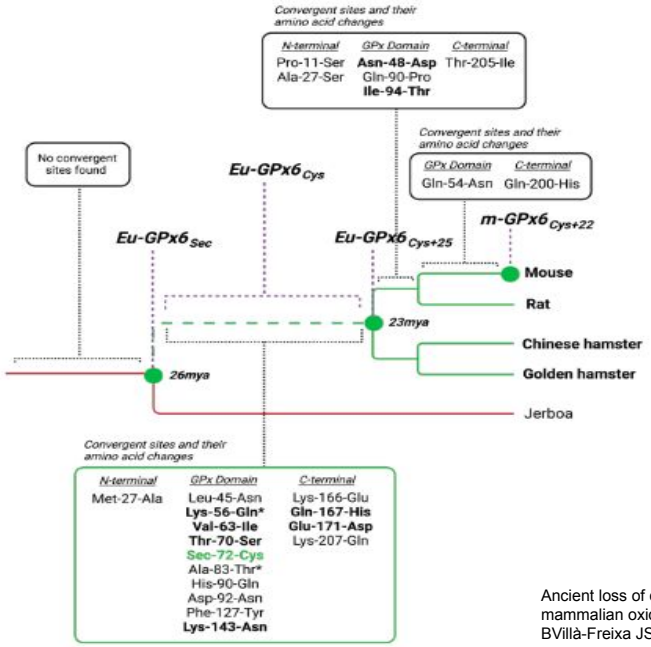
SNPs based on literature

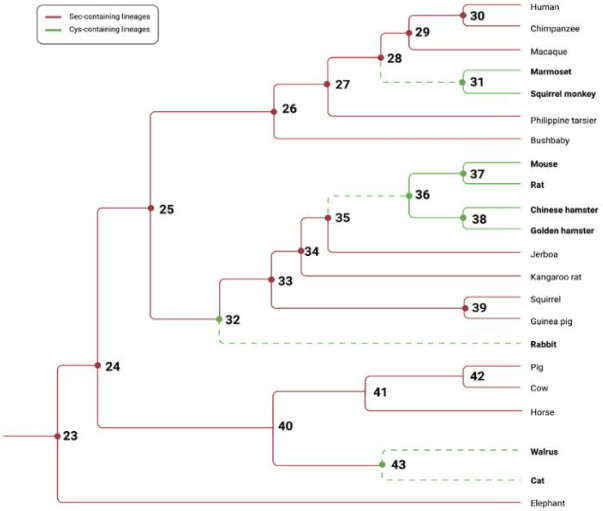
| Polymorphisms | Associated Disease |
|---|---|
| GPX1: Pro198Leu, rs1050450 | Breast, Lung, Colorectal Cancer |
| GPX4: rs713041 | Breast Cancer, Colorectal Cancer |
| GPX3: rs3763013, rs8177412, rs3805435, rs3828599, rs2070593 | Gastric Cancer, Thyroid Cancer |

# SO what do we focus on ?

1. GPX6 appears to lose its peroxidase activity when Sec is replaced by Cys in the active site. Does this loss happen only due to a single mutation or accumulation of mutations?

2. How does the evolutionary trajectory of GPX6 give an insight in terms of the relationship between oxidative stress and cancer progression?

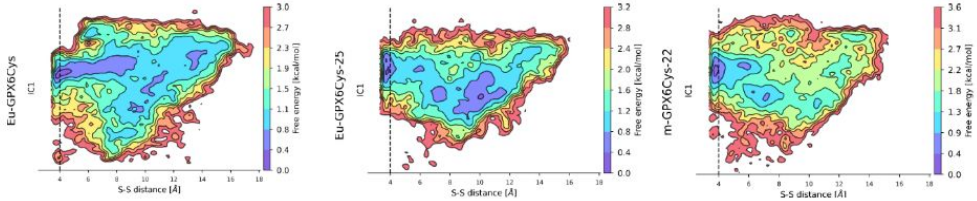


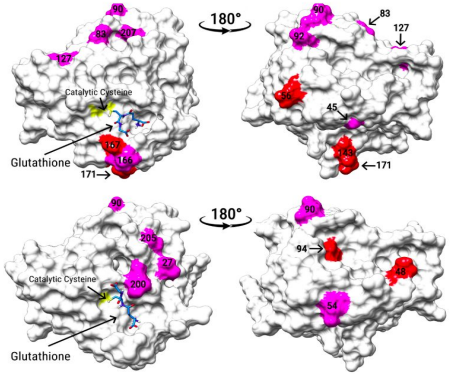

Ancient loss of catalytic selenocysteine spurred convergent adaptation in a mammalian oxidoreductase. Rees JSarangi GCheng QFloor MAndrés AMiguel BVillà-Freixa JSj Arnér ECastellano S. Doi: 10.1101/2023.01.03.522577

GOAL
To discriminate the possible evolutionary pathways that link the ancestral protein with modern one.

# Previous Results




Free energy profiles for the docking of the glutathione dimer to ancestral and modern GPX6 Cys proteins

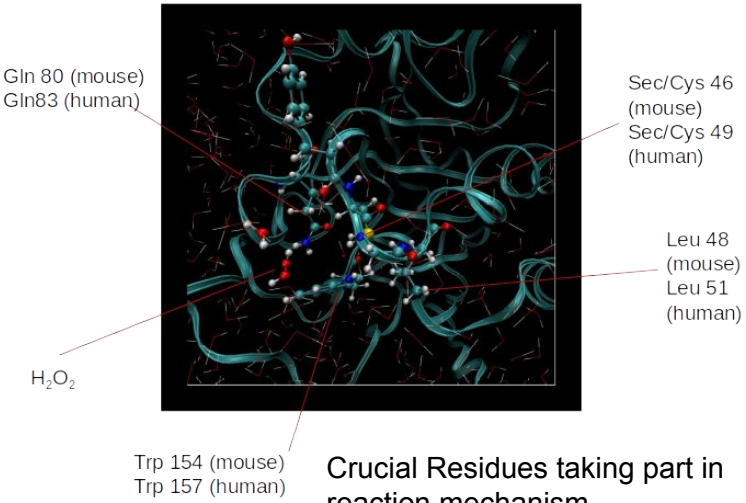



The catalytic cysteine (yellow) is shown with the glutathione best binding energy conformation.

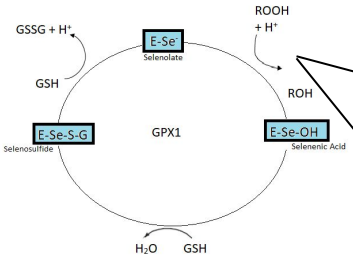
## KEY FINDINGS

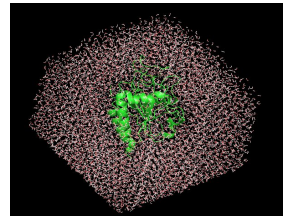
Binding of GSH and overall structures of the enzymes have not been adversely affected by the involvement of Cys.

# Preparation of the systems



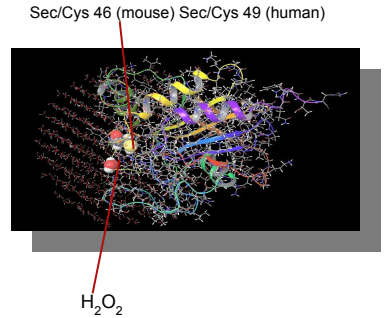

Crucial Residues taking part in reaction mechanism



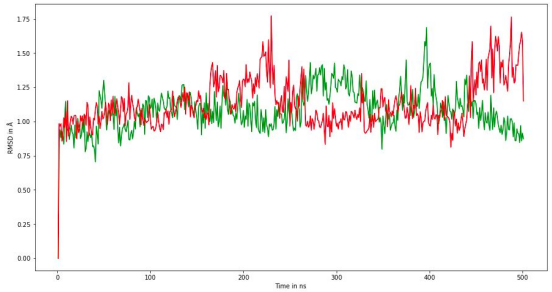
Molecular Dynamics Simulations with Amber

EVB (Empirical Valence Bond) Simulations with Q6 program



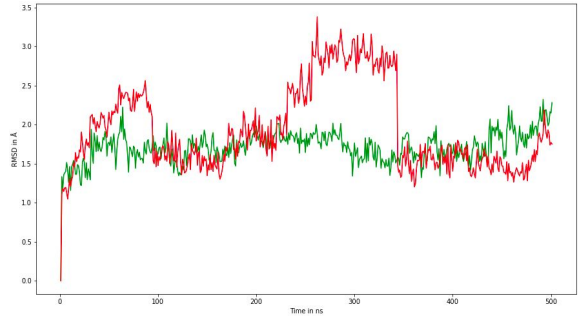
# Current Results

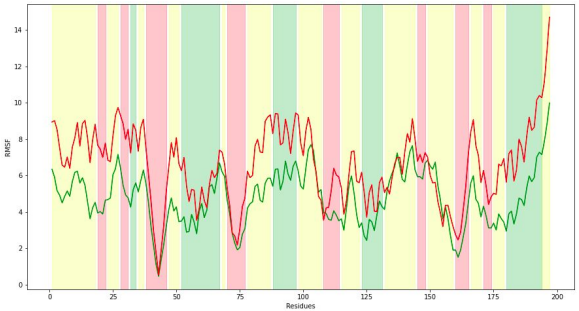
## Mouse





Sec - Green
Cys - Red



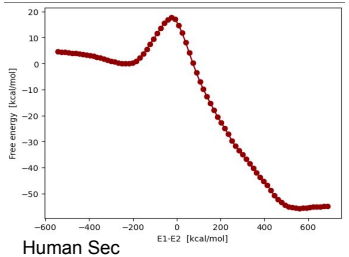

## Human

The RMSD value is lower with Sec than Cys in mouse and human structures.

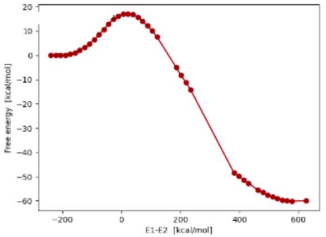
The Root mean square fluctuations are seen more in Cys Mouse and Human residues than the Sec

## Hypothesis

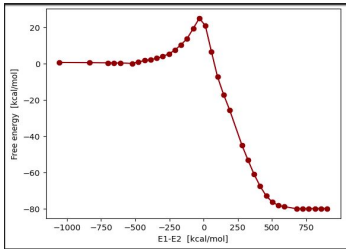
| | |
|---|---|
| Human Sec and Mouse Sec<br>Expected outcome<br>$\Delta g^{+}$ Hsec < $\Delta g^{+}$ Msec | Human Cys and Mouse Cys<br>Expected outcome<br>$\Delta g^{+}$ Mcys < $\Delta g^{+}$ Hcys |
| Human Sec and Human Cys<br>Expected outcome<br>$\Delta g^{+}$ Hsec < $\Delta g^{+}$ Hcys | Mouse sec and Mouse Cys<br>Expected outcome<br>$\Delta g^{+}$ Msec < $\Delta g^{+}$ Mcys |



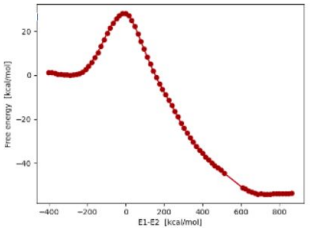

Human Sec




Mouse Sec




Mouse Cys




Human Cys

The plots obtained from EVB calculations correspond to the hypothesis

# A Thank You To



Thesis Supervisor - Dr. Jordi Villà i Freixa

The Computational Biochemistry and Biophysics lab (http://mon.uvic.cat/cbbl)

Co-supervisor – Dr. Vijay Baladhye

Bi-squared Research Group
Bioinformatics and Bioimaging
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